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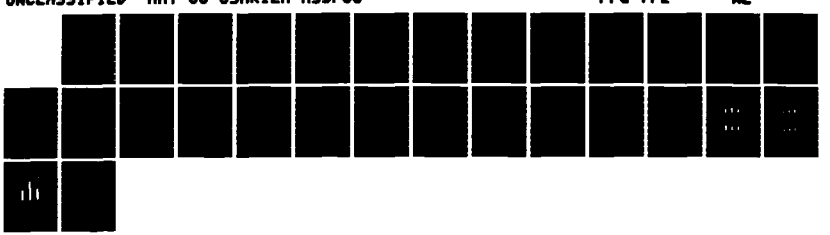

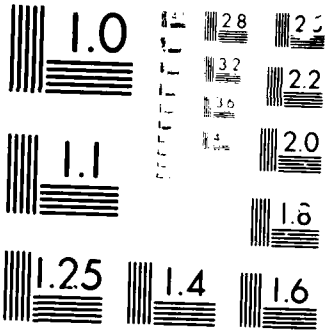
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This study examined the effects of acclimatization to 4300 m altitude on changes in plasma ammonia concentrations with 30-min submaximal (75% $\dot{V}O_2$ max) cycle exercise. Human test subjects were divided into a sedentary (n=6) and active group (n=5). Maximal oxygen uptake ($\dot{V}O_2$ max) was determined at sea level, after acute HA (t 24h) and chronic HA (t=13d), exposure to 4300 m altitude. The $\dot{V}O_2$ max of both groups decreased 32% with acute HA when compared to sea level. In the sedentary group, $\dot{V}O_2$ max was decreased an additional 16% following 13-days residence at 4300 m, while $\dot{V}O_2$ max in the active group showed no further change.

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Plasma ammonia concentration increased (P 0.05) over resting levels immediately following submaximal exercise during sea-level and acute HA exposure in both groups. Immediately following submaximal exercise at chronic HA, the active group showed no increased plasma ammonia accumulation, whereas the post-exercise ammonia in the sedentary group was elevated but to a lesser extent than sea level or acute HA. Thus, post-exercise plasma ammonia concentration is decreased with altitude acclimatization when compared to exercise performed at the same relative intensity at sea level or acute HA. This decrease in ammonia levels may contribute to enhanced endurance performance and altered substrate utilization with exercise following acclimatization to altitude.

# ALTITUDE ACCLIMATIZATION ATTENUATES PLASMA AMMONIA ACCUMULATION DURING SUBMAXIMAL EXERCISE

Patricia M. Young, Paul B. Rock, Charles S. Fulco
Laurie A. Trad, Vincent A. Forte, Jr., and Allen Cymerman

Altitude Research Division
U.S. Army Research Institute of Environmental Medicine
Natick, Massachusetts 01760

Running Head: plasma ammonia at altitude.

Address correspondence to:

Dr. Patricia M. Young
Altitude Research Division
U.S. Army Research Institute of
Environmental Medicine
Natick, Massachusetts 01760
(617) 651-4880

ABSTRACT

This study examined the effects of acclimatization to 4300 m altitude on changes in plasma ammonia concentrations with 30-min submaximal (75% $\dot{V}O_2$ max) cycle exercise. Human test subjects were divided into a sedentary (n=6) and active group (n=5). Maximal oxygen uptake ($\dot{V}O_2$ max) was determined at sea level, after acute HA (t<24h) and chronic HA (t=13d), exposure to 4300 m altitude. The $\dot{V}O_2$ max of both groups decreased 32% with acute HA when compared to sea level. In the sedentary group, $\dot{V}O_2$ max was decreased an additional 16% following 13-days continuous residence at 4300 m, while $\dot{V}O_2$ max in the active group showed no further change. Plasma ammonia concentration increased ($P<0.05$) over resting levels immediately following submaximal exercise during sea-level and acute HA exposure in both groups. Immediately following submaximal exercise at chronic HA, the active group showed no increased plasma ammonia accumulation, whereas the post-exercise ammonia in the sedentary group was elevated but to a lesser extent than sea level or acute HA. Thus, post-exercise plasma ammonia concentration is decreased with altitude acclimatization when compared to exercise performed at the same relative intensity at sea level or acute HA. This decrease in ammonia levels may contribute to enhanced endurance performance and altered substrate utilization with exercise following acclimatization to altitude.

Index Terms: plasma lactate, insulin, glucose, $\dot{V}O_2$ max

## INTRODUCTION

During the first 3 weeks of altitude acclimatization, a dramatic increase in endurance capacity for submaximal exercise has been observed (16). The mechanism of this adapation has not been identified. However, it has been reported that after 18-days residence at 4300 m altitude, alterations occur in energy substrate utilization during exercise. After this period of acclimatization, post-exercise blood lactate levels were decreased and muscle glycogen utilization was reduced; increased utilization of free fatty acid appeared to account for the "glycogen sparing" (28). Similar changes in metabolism have been observed as a result of long-term endurance training (18,20). However, metabolic adaptations to endurance training are associated with increased activity of oxidative enzymes (13), and changes in human skeletal muscle enzyme activities were not observed with short-term altitude acclimatization (29). Thus, an alternative mechanism for the reduction in glycogen utilization with altitude acclimatization must exist.

Ammonia is another metabolite produced by exercising muscle, and reductions in post-exercise ammonia levels have been observed in trained rats (5). Ammonia is not a direct metabolite of the glycolytic pathway, but is produced by the purine nucleotide cycle (PNC) (15). During the operation of the PNC, ammonia is produced by the conversion of adenosine monophosphate (AMP) to inosine monophosphate (IMP). Elevated intracellular ammonia levels have been shown to increase the rate of glycolysis by activation of phosphofructokinase (15) and lead ultimately to an increase in lactate levels by inhibition of pyruvate carboxylase and pyruvate dehydrogenase (8,9,27). Since plasma ammonia and lactate levels in exercising muscle are closely correlated (25), measurement of

ammonia levels following exercise at high altitude may aid in understanding the alterations in energy substrate utilization associated with altitude acclimatization.

The purpose of this investigation was to test the hypothesis that altitude acclimatization would result in decreased ammonia accumulation during submaximal exercise. A decrease in ammonia levels could lead ultimately to a reduction in glycolytic activity, thereby, accounting for decreased glycogen breakdown and decreased lactate accumulation during exercise. In order to separate the effects of altered physical activity and altitude acclimatization, the responses of a sedentary group were compared to a group engaged in a physical exercise regimen.

## METHODS

After being informed of the nature and requirements of the study, 12 healthy male soldiers (20 ± 2 yrs) voluntarily consented to serve as test subjects. One subject left the study during the acute altitude phase. All were sea-level natives who had not been exposed to an altitude greater than 1500 m for at least 6 months prior to the study. The subjects had participated in typical U.S. Army physical training prior to the study, but none were exceptionally well trained. Initially, each subject's maximal $O_2$ uptake ($\dot{V}O_2$ max) was determined on both a rowing and cycling ergometer. From those data, the subjects were matched in pairs. One member of the pair was assigned randomly to the sedentary group, the other to the active group.

The study consisted of a 21-day sea-level phase completed in Natick, Massachusetts, elevation 50 m, and a 14-day altitude phase where subjects

resided on the summit of Pikes Peak, Colorado, elevation 4300 m. Daily caloric intake during the sea level phase averaged 2750 kcal/day and 1750 kcal/day during the altitude phase with 15% of the total kcal from fat; 20%, protein; and 65%, carbohydrate. During the study, there was no difference in average weight loss (4.73±0.62 kg) between groups. During both phases, the active group (n=5) exercised twice daily for 20-min on a rowing ergometer (Concept II, Inc. Morrisville, Vermont, USA) at 75% of the altitude-specific rowing $\dot{V}O_2$ max. The sedentary group (n=6) did not perform any physical exercise other than that associated with normal living activities. Cycling testing was performed on a electronically braked Collins cycling ergometer (Collins, Inc., Braintree, Massachusetts, USA). Cycling and rowing $\dot{V}O_2$ max tests were performed at sea level, once during a 2 h exposure to a simulated altitude of 4300 m in a hypobaric chamber, and again after 13 days of continuous residence at Pikes Peak. In addition, submaximal cycling exercise tests were performed once during the sea level phase (day 19), during the first 24 h at Pikes Peak (acute HA), and on day 14 of residence at Pikes Peak (chronic HA) for 30 min at 75% of the environmentally specific $VO_2$ max.

Venous blood was collected in EDTA from a catheter placed in the median basilic vein before arising on the morning of each submaximal exercise test, immediately before and after submaximal exercise, and following a 30-min and 60-min recovery period. Plasma was separated by centrifugation and analyzed for lactate concentration using an automated analyzer (Model 23L, Yellow Springs Instruments, Yellow Springs, Ohio, USA) and ammonia levels using an enzymatic kit (Sigma Chemical Co., St. Louis, Missouri, USA) within 2 h of collection. The remaining samples were stored in liquid nitrogen (-196°C) until analyzed and

all samples from one subject were analyzed in the same assay to avoid interassay variance. Plasma glucose concentration was determined using an automated analyzer (Beckman, Palo Alto, California, USA). Plasma insulin levels were determined by radioimmunoassay (Serono Laboratories, Inc., Randolph, Massachusetts, USA). Blood urea nitrogen levels were determined by a colorimetric method (Sigma Chemical Co., St. Louis, Missouri, USA). Plasma free fatty acid (FFA) levels were determined by a colorimetric method (Nippin Shoji Kaisha, Ltd., Osaka, Japan) and plasma glycerol levels were determined by an enzymatic kit (Behring Diagnostics, La Jolla, California, USA).

Data were analyzed using a three-way analysis of variance (ANOVA) to determine of factor main effects and interactions were significant. A Tukey's critical difference test was used to identify significant differences between means. Statistical significance was accepted at the $P<0.05$ level. All data are expressed as mean±SEM.

## RESULTS

### MAXIMAL CYCLING EXERCISE TESTING

At sea level, there was no difference between the mean $\dot{V}O_2$ max of the active group (3.82±0.24 L/min) and the sedentary group (3.84±0.22 L/min). Similarly, there was no difference in the mean $\dot{V}O_2$ max between the active and sedentary group with acute HA exposure averaging 2.59±0.09 L/min and 2.57±0.09 L/min, respectively. This represented a decrease of 32% from values obtained at sea level. After 13-days residence at 4300 m, the $\dot{V}O_2$ max of the active group showed no change from acute HA values (2.57±0.07 L/min), while the $\dot{V}O_2$ max of the sedentary group decreased by 16% when compared to the acute HA $\dot{V}O_2$ max to 2.17±0.09 L/min on day 13 at Pikes Peak.

SUBMAXIMAL EXERCISE

Exercise $\dot{V}O_2$. During the 30-min submaximal exercise bout at sea level, mean $\dot{V}O_2$ (2.77 L/min, 72% $\dot{V}O_2$ max) for the active group was significantly higher than during acute HA (1.87 L/min, 73% $\dot{V}O_2$ max) and chronic HA (1.77 L/min, 71% $\dot{V}O_2$ max). There was no difference between submaximal exercise oxygen consumption during acute and chronic HA. For the sedentary group, mean $\dot{V}O_2$ at sea level (2.78 L/min, 73% $\dot{V}O_2$ max) was significantly higher than during acute HA (1.91 L/min, 74% $\dot{V}O_2$ max) and chronic HA (1.62 L/min, 74% $\dot{V}O_2$ max). Also, oxygen consumption at acute HA was significantly ($P<0.05$) greater than chronic HA for the sedentary group. Relative exercise intensity (% $\dot{V}O_2$ max) was not different between groups and was the same for all submaximal tests.

Respiratory Exchange Ratio. There was no significant difference between the active and sedentary subjects in the respiratory exchange ratio (R) during exercise at sea level (Table 1). With acute HA, R was higher than sea level values for both groups, with no significant difference between groups. After 14 days residence at 4300 m, the R value for the active group (1.03±0.06) remained the same as with acute HA; in the sedentary group, R (1.13±0.05) increased significantly over values observed at acute HA. There was no significant difference in minute ventilation ($\dot{V}_E$) for the active group during exercise at sea level, acute HA, or chronic HA. For the sedentary group, there was no significant difference in $\dot{V}_E$ at sea level or acute HA; however, during chronic HA, $\dot{V}_E$ (115.8 L/min) was significantly higher than sea level. The ventilatory equivalent for $O_2$ ($\dot{V}_E/\dot{V}O_2$) for the active group at acute HA and chronic HA was increased approximately 47% when compared to values observed during sea level. For the sedentary group, $\dot{V}_E/\dot{V}O_2$ was increased 64% at acute HA when compared to

sea level. During chronic HA, $\dot{V}_E/\dot{V}O_2$ for the sedentary group increased two-fold over values at sea level with a significant (22%) increase over acute HA values.

Plasma Ammonia Accumulation during Submaximal Exercise and Recovery. Plasma ammonia concentration before and after exercise and recovery are shown in Figure 1 for both groups combined. There were no significant differences in resting plasma ammonia concentrations between sea level, acute HA, and day 13 of residence at HA. After 30-min submaximal cycling exercise, plasma ammonia was increased to 102 μM at sea level and 95 μM at acute HA, representing no difference. Following 13 days residence at 4300 m, post-exercise levels were 54 μM, representing a two-fold decrease compared to sea level and acute HA values. Plasma ammonia returned to pre-exercise levels following 30- and 60-min rest and plasma ammonia during recovery were not different regardless of altitude. Additionally, blood urea nitrogen (BUN) levels were not increased during any exercise bout or recovery (data not shown).

The effect of the physical activity regimen on changes in plasma ammonia concentrations with 75% submaximal exercise and recovery following is shown in Fig. 2. At sea level, acute HA, and chronic HA ammonia levels prior to exercise were not different between groups. Immediately following 30-min submaximal exercise, the sedentary group (Fig. 2A) had mean plasma ammonia concentrations of 92 μM and 95 μM, and the exercised group (Fig. 2B), 106 μM and 83 μM at sea level and acute HA, respectively. Each represents a significant ($P<0.05$) increase over resting values, but no significant difference between groups. During chronic HA, the post-exercise plasma ammonia concentration of the sedentary group averaged 60 μM, representing a significant increase over resting values, but significantly lower than observed for this group following exercise

at sea level or acute HA. Plasma ammonia levels in the active group were unchanged by exercise at chronic HA exposure. Following 30-min rest, there was no difference in ammonia levels in either group when compared to initial values.

Plasma Lactate Levels during Submaximal Exercise and Recovery. Plasma lactate concentration before, immediately after, and following 30-min recovery from submaximal exercise is shown for the sedentary (Fig. 3A) and active (Fig. 3B) groups. Resting plasma lactate concentrations did not differ between groups and were not affected by altitude. Immediately following 30-min submaximal exercise, the sedentary group demonstrated an increase in plasma lactate values to 6.2 mM, 10.4 mM, and 7.9 mM, and the active group, 5.6 mM, 9.1 mM, and 5.3 mM, at sea level, acute HA, and chronic HA, respectively. For both groups, post-exercise plasma lactate levels were increased significantly ($P<0.05$) over values obtained at rest. Also, lactate levels observed at acute HA were higher than sea level and chronic HA values. Between groups there were no differences between lactate values at sea level and acute HA. With chronic HA exposure, post-exercise plasma lactate levels of the active group were lower than values seen in the sedentary group ($P<0.05$). Following 30-min rest at sea level, plasma lactate levels were not different from values observed before exercise in both groups. At acute and chronic HA after resting for 30-min , plasma lactate levels in both groups during recovery (30-min rest) were approximately two-fold higher than values observed initially after recovery at sea level.

Plasma Glucose and Insulin Levels during Submaximal Exercise and Recovery. The effect of submaximal exercise at sea level and high altitude on plasma glucose concentration is shown in Fig. 4. There was no significant difference between groups, and the data were averaged for all test subjects. With exercise

at sea level, the initial plasma glucose averaged 4.4 mM, and there was no significant change with exercise or recovery. With acute HA, the resting glucose concentration, 6.8 mM, was elevated significantly ($P<0.05$) when compared to sea-level values. With acute HA exposure, plasma glucose concentration decreased during exercise to 4.8 mM, but after 30-min recovery, plasma glucose concentration had returned to pre-exercise levels. After 13-days residence at 4300 m, plasma glucose levels were not different from those observed at sea level during rest, exercise, and recovery.

No significant difference in plasma insulin concentration was observed between rest, post-exercise, or recovery insulin values at each altitude or between groups for any exercise bout. At sea level, plasma insulin concentration was 860±49 μU/ml. During acute HA, plasma insulin concentration averaged 1630±201 μU/ml, representing a two-fold increase in plasma insulin concentrations when compared to sea-level values. After 13-days residence at 4300 m, plasma insulin concentration was 890±120 μU/ml which was not different from sea level values.

Effect of Exercise at Altitude on Free Fatty Acid: Glycerol Molar Ratio. Plasma free fatty acid (FFA): glycerol molar ratio was examined immediately before and after submaximal exercise for all subjects was examined (Table 2). There was no difference between resting plasma FFA: glycerol ratio with sea level and acute HA exposure; however, with chronic HA, resting FFA: glycerol ratio was increased ($P<0.05$) over sea level and acute HA. Exercise at sea level and during acute HA had no significant effect on FFA: glycerol molar ratios; however, at chronic HA, the FFA: glycerol ratio decreased significantly with exercise compared to the resting value.

DISCUSSION

In previous investigations of human acclimatization to altitude, the effects of altered or decreased physical activity have not been controlled or quantified. For that reason, in the present investigation, two groups of subjects were studied, a sedentary and a physically active group. The purpose of the exercise regimen followed by the active group was not to improve aerobic fitness, but rather to offset the relatively sedentary lifestyle often assumed by test subjects confined to the summit of Pikes Peak. Rowing ergometry was selected as the mode of activity because it provided exercise for upper and lower extremities, but did not train specifically for cycling exercise. The subjects in the active group followed the exercise regimen throughout the 21-day sea-level phase in order to habituate them prior to the altitude phase. Since 3 days before going to high altitude, the mean $\dot{V}O_2$ max of the two groups were not significantly different, each group began the altitude phase at approximately equal levels of aerobic fitness. Both groups experienced similar decrements in $\dot{V}O_2$ max with acute high altitude exposure (32% compared to sea level) comparable to other studies at 4300 m (30). After 13 days at altitude, the sedentary group experienced an additional decrease in $\dot{V}O_2$ max of 16% when compared to acute HA. The subjects participating in the exercise regimen demonstrated no further change in $\dot{V}O_2$ max between acute high altitude exposure and day 13 of residence at high altitude. The additional decrement in $\dot{V}O_2$ max experienced by the sedentary subjects is similar to that reported to occur with comparable or longer periods of bed rest (20). Although the sedentary subjects did not exercise regularly, they were not confined to bed during this study. It is possible that at extreme altitude, a more rapid "detraining" occurs. This

possibility should be considered when designing studies requiring continuous residence at high altitude.

This study has demonstrated that with acclimatization to 4300 m altitude, post-exercise plasma ammonia concentration was decreased when compared to exercise bouts during sea level and acute HA that were performed at the same relative intensity. Also, subjects maintaining a constant level of aerobic fitness experienced a greater reduction in post-exercise plasma ammonia and lactate accumulation with acclimatization to altitude when compared to sedentary subjects. This is consistent with reports of decreased accumulation of blood ammonia during exercise in endurance-trained rats (5). Decreased exercise accumulation of ammonia may contribute to increased endurance observed in other chronic HA studies.

Alterations in ammonia accumulation during exercise may contribute to improvements in endurance capacity through alterations in energy substrate utilization. Ammonia and other metabolites of the purine nucleotide cycle modulate the activity of key enzymes in the breakdown of glycogen and oxidation of glucose (2). Ammonia accumulation during exercise leads to the activation of phosphofructokinase (PFK) and inhibition of pyruvate dehydrogenase and pyruvate carboxylase. Decreased pyruvate oxidation leads ultimately to increased conversion of pyruvate to lactate. Conversely, decreased levels of ammonia would favor a lower glycolytic rate since PFK would not be activated, and pyruvate oxidation would proceed with shunting of metabolites into the TCA cycle rather than lactate accumulation. Since isocitrate dehydrogenase is inhibited by ammonia (14), a decrease in ammonia concentration would lead to enhanced TCA cycle activity as well. Thus, decreased ammonia levels would improve endurance by decreasing lactate accumulation and enhancing TCA cycle activity.

Previous research has demonstrated that with acclimatization to high altitude, glycogen stores were spared in exercising muscle with an apparent shift to oxidation of FFA for energy (28). In this study, post-exercise plasma lactate values were decreased with chronic HA exposure when compared to acute HA although exercise was performed at the same intensity. Also plasma FFA: glycerol ratio was significantly decreased immediately following exercise with chronic HA only, an indication of enhanced FFA uptake and utilization. It is interesting to note that plasma FFA: glycerol ratio was higher before exercise at chronic HA only; thus increased FFA were available to enter the muscle by mass action at the onset of exercise. Therefore, it appears that carbohydrate utilization was diminished and FFA uptake enhanced with acclimatization.

In the present study, immediately following exercise (75% of the environmental $\dot{V}O_2$ max) at acute HA ($t<24h$), glucose concentration was significantly decreased and plasma lactate accumulation was greater than observed at sea level. This occurred when plasma insulin levels were approximately two-fold higher than sea level or chronic HA. These findings are in contrast to those of Sutton in which post-exercise plasma glucose was elevated and insulin was lower following acute ($t<3h$) hypobaric exposure when compared to sea level (22). In that study, the subjects exercised at the same absolute workload that was estimated to be between 30-50% of the sea level $\dot{V}O_2$ max at sea level and 80% of sea level max during acute hypoxia. It is possible that longer exposure time and exercise at the same relative workload may exert different effects. In the present study, with increased ammonia accumulation during exercise with acute HA, elevated insulin may enhance glucose uptake by the muscle leading ultimately to increased lactate accumulation.

It is possible that decreased ammonia accumulation can lead to decreased perceptions of fatigue (7). The sedentary subjects showed an increase in $\dot{V}_E/\dot{V}O_2$ with submaximal exercise at altitude that was not observed in the physically active group. Since ammonia accumulation during exercise is correlated with local and central perceptions of fatigue (7) and development of exercise-induced hyperpnea (19,23,26), it is possible that decreased ammonia accumulation may contribute to a decrease in the perception of exercise exertion and thereby account for the reported increased endurance capacity observed with altitude acclimatization (16).

In summary, post-exercise plasma ammonia concentrations are decreased with acclimatization to high altitude when compared to exercise bouts performed at the same relative intensity at sea level or acute HA. It is possible that decreased ammonia accumulation leads to enhanced performance and alterations in energy substrate utilizations that have been observed with altitude acclimatization.



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TABLE 1

R, $\dot{V}_E$, and $\dot{V}_E/\dot{V}O_2$ During Submaximal Exercise on the Cycle Ergometer

| | | R | $\dot{V}_E$ | $\dot{V}_E/\dot{V}O_2$ |
|---|---|---|---|---|
| Sedentary | Sealevel | 0.84 | 86.12 | 32.00 |
| | | ±0.01 | ±6.29 | ±1.29 |
| | Acute HA | 1.05* | 103.92 | 52.40* |
| | | ±0.01 | 10.07 | ±1.91 |
| | Chronic HA | 1.13*+ | 115.83* | 63.74*+ |
| | | ±0.051 | ±9.78 | ±3.20 |
| Active | Sealevel | 0.84 | 97.28 | 34.80 |
| | | ±0.02 | ±12.89 | ±3.10 |
| | Acute HA | 1.03* | 99.36 | 48.67* |
| | | ±0.01 | ±8.57 | ±4.55 |
| | Chronic HA | 1.03* | 95.76 | 54.00* |
| | | ±0.06 | ±9.98 | ±4.55 |

Values are mean ± SE of measurements obtained during the last 10 minutes of a 30 minute submaximal exercise bout (n=10). R, respiratory exchange ratio; $\dot{V}_E$, minute ventilation (L/min), $\dot{V}_E/\dot{V}O_2$, ventilatory equivalent for $O_2$; HA, high altitude; acute, t<24h; chronic, t=13d.

* $p<0.05$ from sea level.

+ $p<0.05$ from acute HA.

TABLE 2

Effect of Submaximal Cycling Exercise on FFA: Glycerol Molar Ratio

| | Before Exercise | After Exercise |
|---|---|---|
| Sea Level | 2.98 ± 0.81 | 1.82 ± 0.46 |
| Acute HA | 3.42 ± 0.68 | 2.51 ± 0.38 |
| Chronic HA | 4.61 ± 0.77 | 2.83 ± 0.86* |

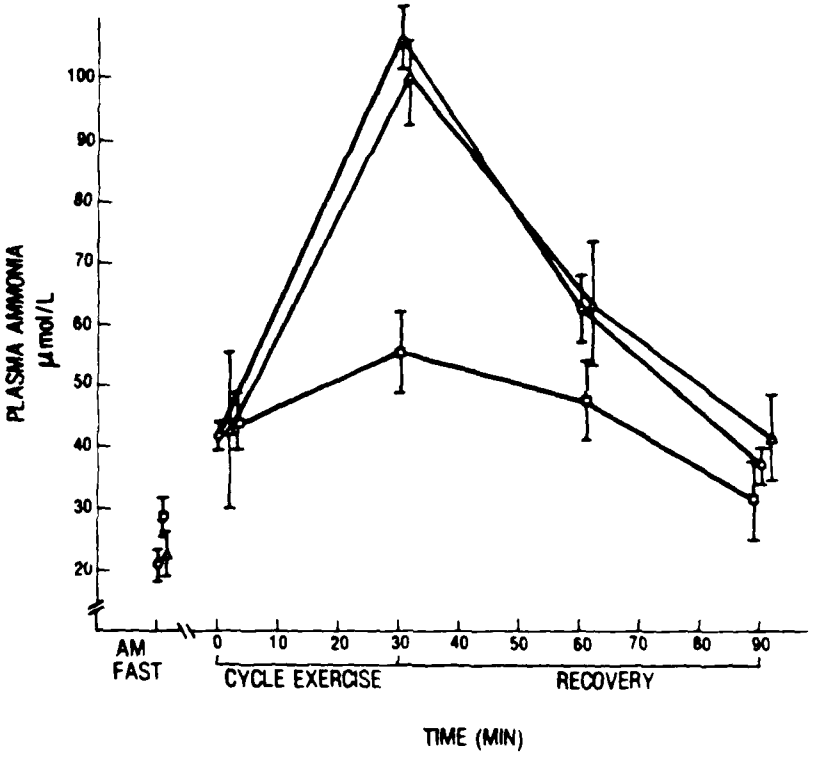
Data expressed as mean±SE for all subjects (n=11). *P<0.05 from before exercise. HA, high altitude; acute, t<24h; chronic, t=13d.

Figure 1. Effect of submaximal cycling exercise at altitude on plasma ammonia concentration. Plasma ammonia levels (mean±SE) were measured after an overnight fast, before and immediately following exercise, and after 30 and 60 min recovery at sea level (o), acute high altitude (Δ), and chronic high altitude (□) for all test subjects; acute t<24h; chronic t=13d.

Figure 2. Effect of physical activity on plasma ammonia levels following submaximal cycling exercise. Plasma ammonia levels (mean±SE) are shown for the sedentary group (A, n=6) and the exercise trained group (B, n=6). HA, high altitude; acute, t<24h; chronic, t=13d; rest, before exercising; exercise, after exercise; recovery, 30-min post exercise.

Figure 3. Effect of physical activity on plasma lactate levels following submaximal cycling exercise. Plasma lactate levels (mean±SE) are shown for the sedentary group (A, n=6) and the exercise trained group (B, n=5). HA, high altitude; acute, t<24h; chronic, t=13d; rest, before exercise; exercise, after exercise; recovery, 30-min following exercise.

Figure 4. Effect of submaximal cycling exercise at altitude on plasma glucose levels. Data expressed as mean±(SE) for all subjects (n=11). HA, high altitude; acute, t<24h; chronic, t=13d; rest, before exercise; exercise, after exercise; recovery, 30-min after exercise.

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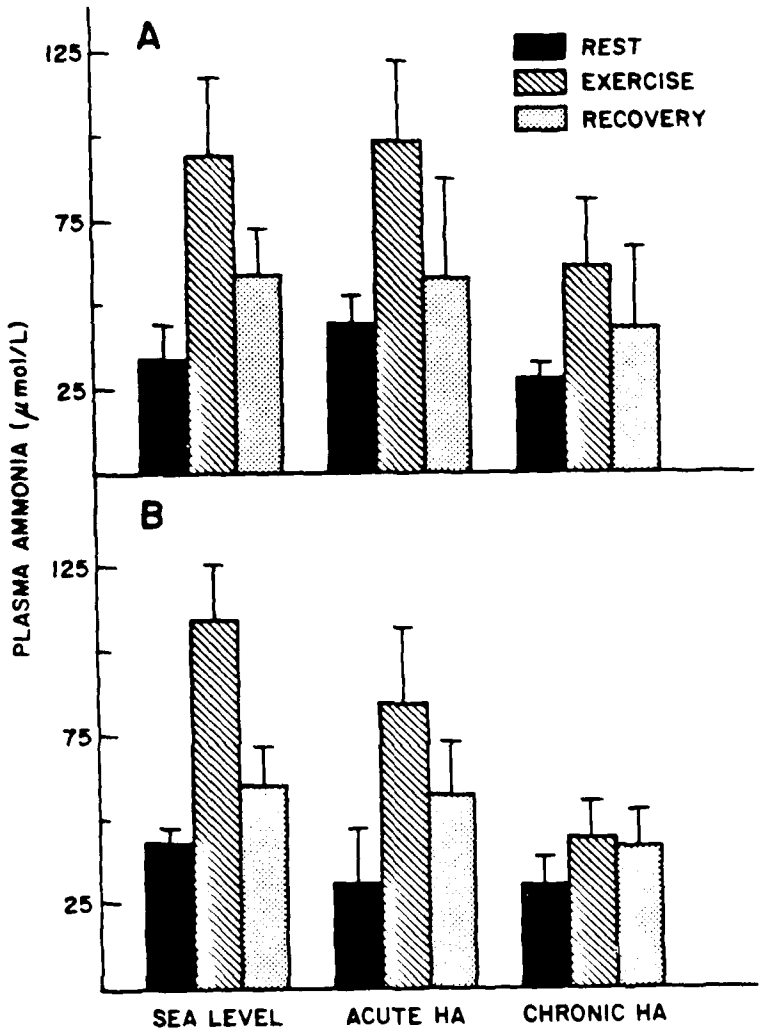


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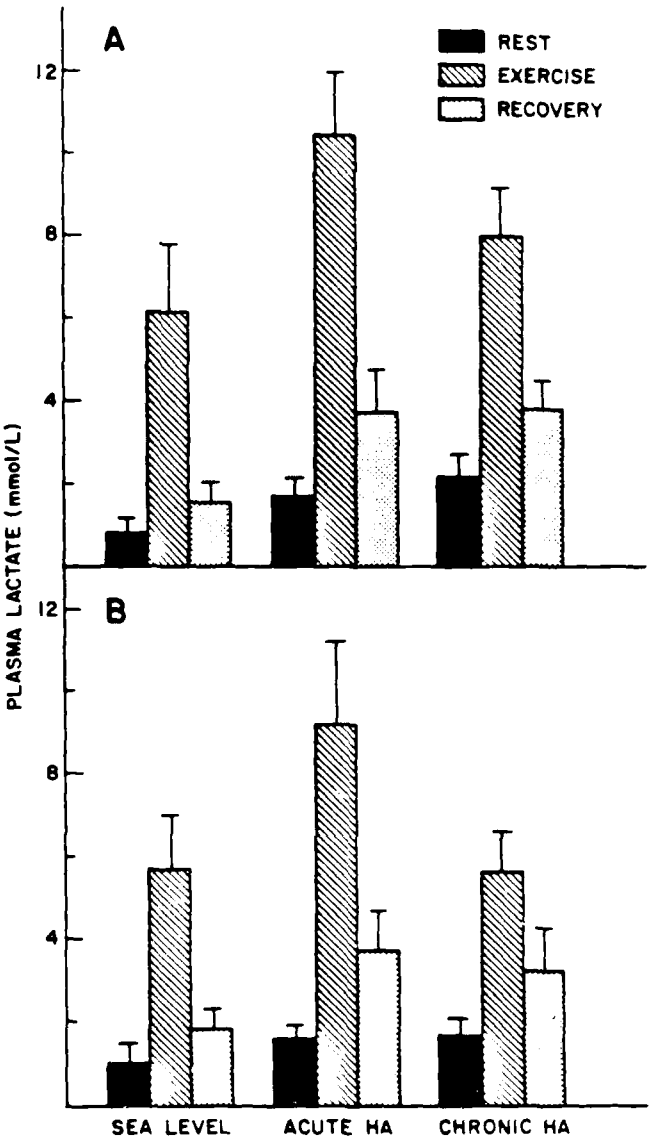


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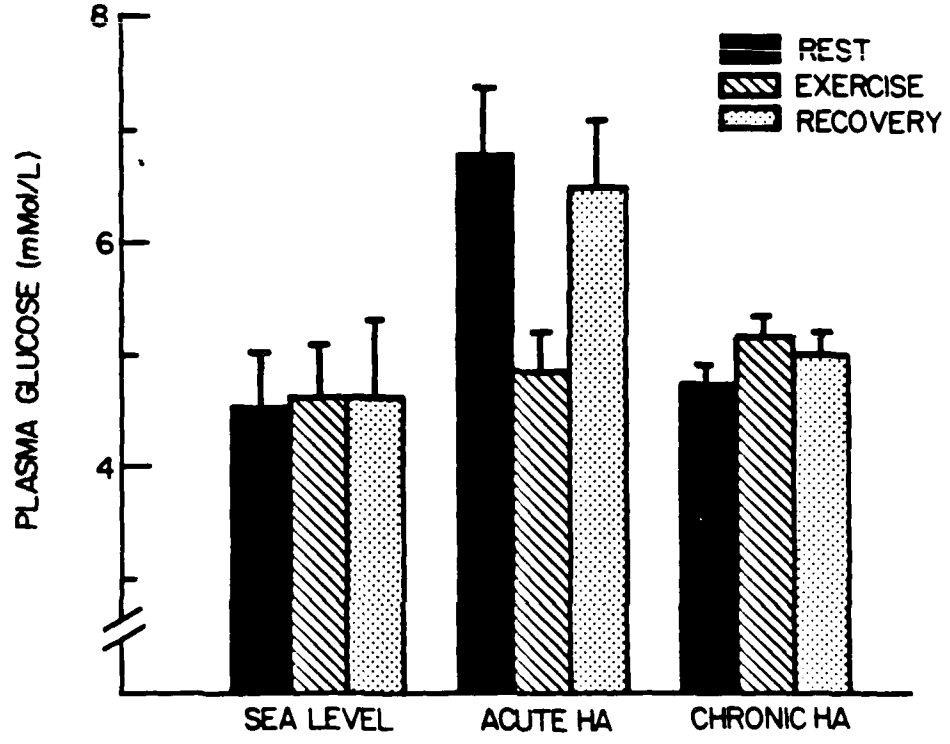


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